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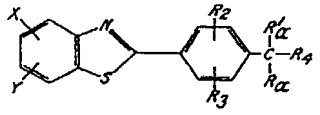
(54) BENZOTHIAZOLE-PHENYL-ACETIC ACID COMPOUNDS

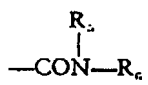
(71) We, MERCK & CO INC, a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with 4-(benzothiazol-2-yl)phenylacetic acids, alcohols, esters and amides, and nontoxic pharmaceutically acceptable salts thereof, processes for their production, and pharmaceutical compositions containing them.

It has been discovered that anti-inflammatory, analgesic and antipyretic activity, including the relief and treatment of pain and fever not symptomatically related to an inflammatory indication, are exhibited by certain compounds having the general formula



in which R_1' is a hydrogen atom or a C_{1-3} alkyl radical and R_6 is a hydrogen atom or R_6' and R_1 together represent a methylene or C_{2-3} alkylidene radical; R_2 is a hydrogen or halogen atom or a hydroxy, C_{1-3} alkoxy, mercapto, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, nitro, amino, di(C_{1-3} alkyl)amino, C_{1-3} alkanoylamino, sulfamoyl or sulfo radical; R_3 is a hydrogen or halogen atom or a C_{1-3} alkoxy, nitro, hydroxy, or amino radical; X is a hydrogen or halogen atom or a di(C_{1-3} alkyl) amino, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, nitro, amino, or C_{1-3} alkyl radical; Y is a hydrogen or halogen atom or a di(C_{1-3}alkyl)amino, C_{1-3} alkylamino, or C_{1-3} alkoxy radical, R_4 is a carboxy or hydroxymethyl radical or a radical of formula —COOR, —COOM or



where R is C_{1-3} alkyl, C_{1-3} alkenyl, C_{4-7} cycloalkenyl, phenyl, phenyl-(C_{1-3} alkyl), (C_{1-3} alkoxy)-(C_{1-3} alkyl), C_{1-3} hydroxyalkyl, or di(C_{1-3} alkyl)amino-(C_{1-3} alkyl) radical; M is a pharmaceutically acceptable non-toxic anion; R_5 is a hydrogen atom

[Price 25p]

or a C_{1-3} alkyl, phenyl-(C_{1-3} alkyl), phenyl, or C_{3-7} cycloalkyl radical and $R_{4'}$ is a hydrogen atom or a C_{1-3} alkyl radical.

When R_2, R_3, X or Y is a halogen atom, it is preferably chlorine or fluorine; when R_2, X or Y is di(C_{1-3} alkyl) amino, the alkyl residues can be similar or dissimilar; when R (in R_4) is phenyl-(C_{1-3} alkyl), it is preferably benzyl.

Preferably R_2 and R_3, which are the same or different, is hydrogen, fluorine or chlorine, and R_4 is —COOH or —COOM, especially when X is hydrogen, fluorine of chlorine, C_{1-3} alkoxy, or C_{1-3} alkyl, but particularly hydrogen; Y is hydrogen, fluorine, chlorine or C_{1-3} alkoxy, but particularly hydrogen; $R_{4'}$ is hydrogen or methyl and R_n is hydrogen.

Specific members of this class which have been found the highly effective anti-inflammatory agents include:

4-(benzothiazol-2-yl)-2-fluorophenylacetic acid,

4-(benzothiazol-2-yl)phenylacetic acid and

2-[4-(benzothiazol-2-yl)phenyl]propionic acid.

With regard to the last compound, in addition to the racemate and levo isomer, of particular interest is the "d" (dextro) isomer; (d)-2-[4-benzothiazol-2-yl)phenyl]-propionic acid.

The new compounds of the present invention are those of Formula I but with the exception of 4-(benzothiazol-2-yl)phenylacetic acid and its amide, i.e. the compounds in which R_4 is carboxy or carbamoyl (—COOH or $CONH_2$) and all the other variables are hydrogen.

The term pharmaceutically acceptable anion signifies those derived from pharmaceutically acceptable inorganic and organic bases. Suitable anions include those of alkali metals such as sodium, potassium or lithium, magnesium, alkaline-earth metals such as calcium, ammonium and organic amines such as ethylamine, triethylamine, ethanolamine, diethanolamine, diethylaminoethanol, ethylenediamine, benzylamine, procaine, pyrrolidine, piperidine, morpholine, 1-ethyl-piperidine and 2-piperidino ethanol. When the cation is multivalent, M in the formula represents one equivalent of the cation, e.g. $\frac{1}{2}[Mg^{++}]$.

Benzothiazoles of Formula I are of value in the treatment of arthritic and dermatological disorders or like conditions responsive to anti-inflammatory drugs. In general they are indicated for a wide variety of conditions where one or more of the symptoms of inflammation, fever and pain are manifested. Included within this category are diseases such as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis, rheumatic fever and inflammatory conditions of the ocular system. As indicated above compounds of Formula I also possess a useful degree of analgesic and antipyretic activity.

For these purposes the compounds may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral, as used herein, includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs and cats, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any known method for the manufacture of pharmaceutical compositions and such compositions may contain one or more sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatine or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be used.

Formulations for oral use may also be presented as hard gelatine capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatine capsules where the active

ingredient is mixed with water or an oil medium, for example arachis oil, peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, e.g. a naturally-occurring phosphatide, for example lecithin, condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycethanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate. The said aqueus suspensions may also contain one or more preservatives, for example ethyl or n-propyl *p*-hydroxy benzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occuring phosphatides, for example soya bean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil may be used including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectibles.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions containing the anti-inflammatory agents are used.

Dosage levels of the order of 0.5 mg. to 140 mg. per kilogram of body weight per day are useful in the treatment of the above indicated conditions (25 mg.—7 gm. per patient per day). For example, inflammation is effectively treated and antipyretic and analgesic activity manifested by the administration of from 0.1 to 50 mg. of the

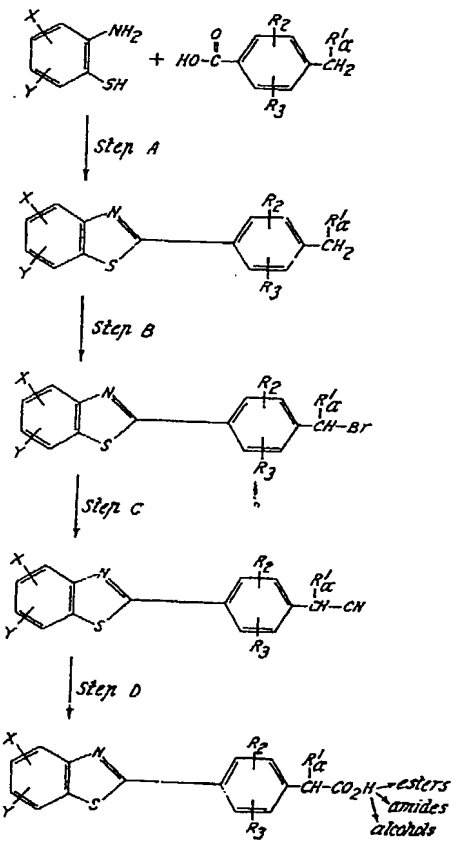
compound per kilogram of body weight per day (5 mg. to 2.5 gms. per patient per day). Advantageously, from 1 mg. to 15 mg. per kilogram of body weight per daily dosage produces highly effective results (50 mg. to 1 gm. per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example a formulation intended for the oral administration of humans may contain from 5 mg. of active agent compounded with an appropriate and convenient amount of carrier material which may vary from 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from 25 mg. to 500 mg. of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Most of the novel compounds of this invention may be prepared as shown by the following scheme:

REACTION SCHEME I



where X, Y, R_2, R_3 and R_1' are as previously defined.

The following is a particular description of each of the steps above:

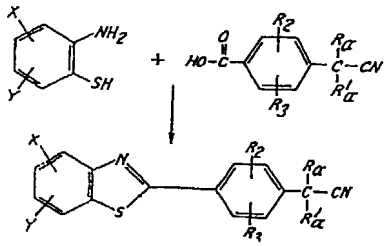
Step A — Reaction of an appropriate o-aminothiophenol with an appropriate benzoic acid in polyphosphoric acid and an inert organic solvent such as chloroform, toluene or benzene, at moderate temperature for 1—3 hours or in polyphosphoric acid at elevated temperatures (about 250°C.) to yield the corresponding alkylphenylbenzothiazole.

Step B — Treatment of the alkylphenyl benzothiazole formed in Step A with N-bromosuccinimide in refluxing carbon tetrachloride, preferably in the presence of a catalytic amount of dibenzoyl peroxide, to give the corresponding bromoalkylphenyl benzothiazole.

Step C — Treatment of the bromoalkylphenyl benzothiazole formed in Step 3 with sodium cyanide in DMSO at 60—70°C. for 1—3 hours to give the corresponding cyanoalkylphenyl benzothiazole.

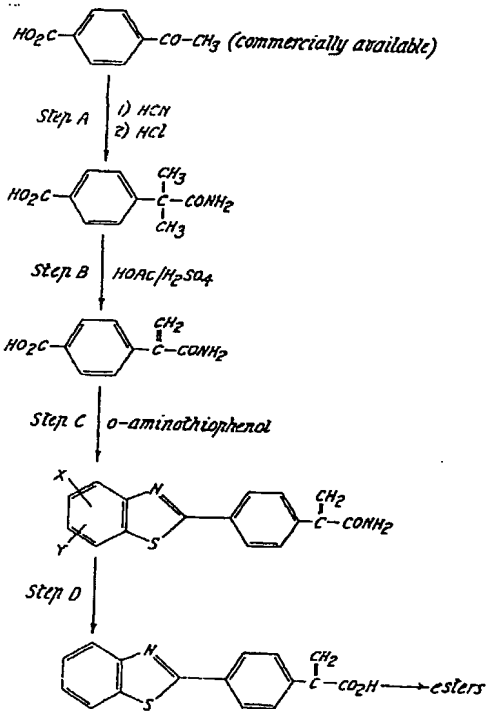
Step D — Acid hydrolysis ofthe cyanoalkylphenyl benzothiazole formed in Step C by heating for about 1 hour at 85—95°C. in concentrated hydrochloric acid to give the desired benzothiazole phenyl acetic acid.

Compounds of Formula I are most readily prepared by starting with a preformed phenylacetonitrile, if available, as follows:



The reaction conditions for the step shown are identical with that described for previous Step A. Conversion of the nitrile to the product of Formula I proceeds exactly as described in previous Step D.

Compounds which have an alkylidene linkage, particularly a methylene linkage, at the α-position of the acid side chain can be prepared according to the following process.



The nontoxic pharmaceutically acceptable salts of the acid can be prepared from the acid by any of the well known methathesis procedures. For example, the acid can be reacted with an inorganic base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide or barium hydroxide.

The compounds of this invention in which R_1 is a COOR group, i.e. esters, are prepared by any esterification procedure using an esterifying agent containing the appropriate R_2 group. For example, the acetic acid compounds of this invention may be reacted with the appropriate C_{1-5} alkanol (preferably methanol) in the presence of a strong acid, such as hydrochloric acid, sulfuric acid or *p*-toluenesulfonic acid, to form the desired R_1 compound. The methyl ester (R_2 = methoxycarbonyl) can also be prepared by the treatment ofthe acid with diazomethane.

The compounds of this invention in which R_1 is a

$$\begin{array}{c} R_5 \\ | \\ -CON-R_6 \end{array}$$

group, i.e. amides, may be prepared by any suitable amidation reaction. For example, the acetic acid compound (preferably the methyl or ethyl ester or acid halide) may be reacted with ammonia, ammonium hydroxide, or an amine compound, at any suitable temperature (room temperature to reflux). When the unsubstituted amide is desired, it is preferred to prepare it through partial hydrolysis of the intermediate acetonitriles by conventional means.

The alcohols may be formed from the corresponding acids using well known reductive techniques. Members of this class include:
4-(benzothiazol-2-yl)-2-fluorophenylethanol,
2-[4-benzothiazol-2-yl-phenyl]propanol.

The following examples are used by way of illustration of the invention. Example 1 is concerned with a physiologically active cpd that is not novel.

EXAMPLE 1.

2-[4-(Benzothiazol-2-yl)phenyl]acetic acid

Step A: *Preparation of 2-[4-benzothiazol-2-yl)phenyl]acetonitrile*

To a mixture of 1.0 gm. of *o*-aminothiaphenol, 10 gm. of polyphosphoric acid and 30 cc. of chloroform is added 1.5 gm. of *p*-cyanomethylbenzoic acid. The reaction mixture is refluxed for 45 minutes during which time solution occurs. The mixture is then concentrated *in vacuo* and ice water added Neutralization with sodium bicarbonate is carried out followed by extraction with methylene chloride. The combined methylene chloride extracts are dried and concentrated to give crude product. Recrystallization from methanol gives 0.65 gm. of 2-[4-(benzothiazol-2-yl)phenyl]acetonitrile, m.p. 157—159°C.

Step B: *Preparation of 2-[4-(benzothiazol-2-yl)phenyl]acetic acid*

A mixture of 0.6 gm. of 2-[4-benzothiazol-2-yl)phenyl]acetonitrile and 25 cc. of concentrated hydrochloric acid is heated on the steam bath for 1 hour during which time a clear solution gradually forms. Upon cooling, a precipitate forms which is collected by filtration. The precipitate is washed with water, air dried and recrystallized from methanol to give 0.49 gm. of 2-[4-benzothiazol-2-yl)phenyl]acetic acid, m.p. 181—184°C.

EXAMPLE 2.

2-[4-(Benzothiazol-2-yl)-phenyl]propionic acid

Step A: *Preparation of 2-(4-Ethylphenyl)benzothiazole*

A mixture of 9.0 gm. of 4-ethylbenzoic acid, 7.5 gm. of *o*-aminothiophenol and 125 cc. of polyphosphoric acid is heated at 250°C. for 4 hours. At the end of this time the reaction mixture is cooled to about 100°C. and poured into ice-water. The resulting mixture is extracted well with methylene chloride. The combined methylene chloride extracts are washed with water, dried and concentrated to yield the crude prpduct. Chromatography on 500 gm. of silica gel and elution with methylene chloride gives 4.5 gm. of 2-(4-ethylphenyl)benzothiazole.

Step B: *Preparation of 2-[4-(1-bromoethyl)phenyl]benzothiazole*

A mixture of 4.4 gm. of 2-(4-ethylphenyl)benzothiazole and 3.5 gm. of N-bromosuccinimide in 200 cc. of carbon tetrachloride is refluxed for half an hour. The reaction

mixture is then filtered to remove succinimide and the filtrate concentrated to yield crude product. Chromatography on silica gel and elution with methylene chloride gives 4.4 gm. of pure 2-[4-(1-bromoethyl)phenyl]benzothiazole.

Step C: *Preparation of 2-[4-(benzothiazol-2-yl)-phenyl]propionitrile*

A mixture of 4.4 gm. 2-[4-(1-bromoethyl)phenyl]benzothiazole in 45 cc. of dimethylsulfoxide is cooled in an ice bath and 3.0 gm. of powdered sodium cyanide is added. After ten minutes the ice bath is removed and the reaction mixture is allowed to warm to room temperature. After 4 hours the reaction mixture is poured into a mixture of benzene-ether and diluted hydrochloric acid. The organic layer is separated, washed well with water, dried and concentrated. Chromatography of the residue on 500 gm. of silica gel and elution with methylene chloride gives 2.4 gm. of 2-[4-(benzothiazol-2-yl)phenyl]propionitrile.

Step D: *Preparation of 2-[4-(benzothiazol-2-yl)phenyl]propionic acid*

A mixture of 2.4 gm. of 2-[4-(benzothiazol-2-yl)phenyl]propionitrile and 75 cc. of concentrated hydrochloric acid is heated on the steam bath for one hour. The reaction mixture is filtered into ice water and the resulting precipitate is separated by filtration and washed with water and then with 25 cc. of ice-cold methanol to give 1.4 gm. of 2-[4-(benzothiazol-2-yl)phenyl]propionic acid, m.p. 178—181°C.

EXAMPLE 3.

2-[4-(Benzothiazol-2-yl)-2-fluorophenyl]acetic acid

Step A: *Preparation of 2-(3-fluoro-4-methylphenyl)benzothiazole*

A mixture of 10 gm. 3-fluoro-4-toluic acid, 9.0 gm. of *o*-aminothiophenol and 125 cc. of polyphosphoric acid is heated for 4 hours at 250°C. with mechanical stirring. The reaction mixture is cooled to about 100°C. and poured into ice water. The resulting mixture is extracted well with methylene chloride. The combined methylene chloride extracts are washed well with water, dried and concentrated. Recrystallization from methanol gives 12.2 gm. of 2-(3-fluoro-4-methylphenyl)benzothiazole, m.p. 97—99°C.

Step B: *Preparation of 2-(4-bromomethyl-3-fluorophenyl)benzothiazole*

A mixture of 12.2 gm. of 2-(3-fluoro-4-methylphenyl)benzothiazole and 10.5 gm. of N-bromosuccinimide is refluxed for 5 hours in 400 cc. of carbontetrachloride. Several portions of benzoyl peroxide (*ca.* 50 mg.) were added during the course of the reaction. After reaction was complete the mixture is filtered to remove succinimide. The filtrate is concentrated, petroleum ether added and 21.2 gm. of 2-(4-bromomethyl-3-fluorophenyl)benzothiazole collected by filtration.

Step C: *Preparation of 2-[4-(benzothiazol-2-yl)-2-fluorophenyl]acetonitrile*

A mixture of 18 gm. of 2-(4-bromomethyl-3-fluorophenyl)benzothiazole and 30 gm. of sodium cyanide in 900 cc of methanol is refluxed for thirty minutes and then poured into acidified ice water. The precipitate is collected and air dried to give 11.4 gm. of crude material. Chromatography on 600 gm. of silica gel and elution with methylene chloride gives 4.9 gm. of pure product and 3.0 gm. of slightly impure material.

Step D: *Preparation of Methyl 2-[4-(benzothiazol-2-yl)-2-fluorophenyl]acetate*

A mixture of 4.8 gm. of 2-[4-(benzothiazol-2-yl)-2-fluorophenyl]acetonitrile and 200 ml. of concentrated hydrochloric acid is heated for thirty minutes on the steam bath. During this time solution of the starting material gradually occurs followed by the formation of a precipitate. After one half hour the mixture is cooled in an ice bath and the yellow precipitate is collected by filtration. The yield is 5 gm. of crude material which melts over a range finally decomposing at 195°C. Recrystallization from methanol gives light yellow crystals melting at 98—100°C. Analysis and NMR indicate the product to be methyl 2-[4-(benzothiazol-2-yl)-2-fluorophenyl]acetate.

Step E: *Preparation of 2-[4-(Benzothiazol-2-yl)-2-fluorophenyl)acetic acid*

A mixture of 1.5 gm. of methyl 2-[4-(benzothiazol-2-yl)-2-fluorophenyl)acetate and 0.5 gm. of sodium hydroxide in 400 cc methanol and 50 cc of water is stirred for one half hour with slight heating to effect solution. The reaction mixture is then concentrated *in vacuo* and dissolved in 125 cc of water and filtered. The filtrate is acidified with acetic acid and the resulting precipitate collected by filtration and air dried. Recrystallization from toluene gives 0.89 gm. of 2-[4-(benzothiazol-2-yl)-2-fluorophenyl)acetic acid, m.p. 175—178°C.

Carrying out the procedure of Example 3, Steps A through E, but substituting for the *o*-aminothiophenol and 3-fluoro-4-toluic acid of Step A, equivalent amounts of the *o*-aminothiophenols and toluic acids identified in Table I, there are produced the corresponding 4-(benzothiazol-2-yl)phenylacetic acids also identified in Table I, in accordance with Reaction Scheme I previously described.

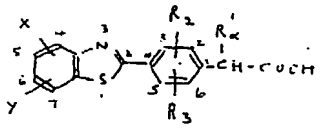


TABLE I

Example	X	Y	R_2	R_3	R'_α
4	5–Cl	H	H	H	H
5	6–Cl	H	H	H	CH_3–
6	7–Cl	H	H	H	CH_3–
7	6–$(CH_3)_2N$–	H	H	H	H
8	5–CH_3O–	H	H	H	H
9	6–CH_3O–	H	H	H	CH_3–
10	5–CH_3S–	H	H	H	H
11	5–O_2N–	H	H	H	CH_3–
12	6–O_2N–	H	H	H	H
13	5–Cl	6–Cl	H	H	H
14	5–C_3H_7–	H	H	H	CH_3–
15	5–$(CH_3)_2N$–	6–$(CH_3)_2N$–	H	H	CH_3–
16	5–Cl	6–$(CH_3)_2N$–	H	H	CH_3–
17	4–CH_3O–	6–Cl–	H	H	CH_3–
18	4–Cl–	6–Cl–	H	H	H
19	5–CH_3O–	6–$(CH_3)_2N$–	H	H	H
20	6–C_2H_5O–	H	H	H	H
21	5–CH_3O–	6–CH_3NH–	H	H	H
22	4–O_2N–	6–CH_3O–	H	H	H
23	5–Cl–	7–Cl–	H	H	H
24	5–CH_3O–	6–CH_3O–	H	H	H
25	5–Cl	H	2–F–	H	H
26	6–Cl	H	2–F–	H	H
27	7–Cl	H	2–F–	H	H
28	6–$(CH_3)_2N$–	H	2–F–	H	H
29	5–CH_3O–	H	2–F–	H	H
30	6–CH_3O–	H	2–F–	H	H
31	5–CH_3S–	H	2–F–	H	H
32	5–O_2N–	H	2–F–	H	H
33	6–O_2N–	H	2–F–	H	H

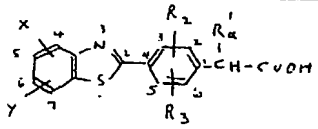


TABLE I (Continued)

Example	X	Y	R_2	R_1	R'_α
34	5–Cl	6–Cl	2–F–	H	H
35	5–C_3H_7–	H	2–F–	H	H
36	5–$(CH_3)_2N$–	6–$(CH_3)_2N$–	2–F–	H	H
37	5–Cl	6–$(CH_3)_2N$–	2–F–	H	H
38	4–CH_3O–	6–Cl–	2–F–	H	H
39	4–Cl–	6–Cl–	2–F–	H	H
40	5–CH_3O–	6–$(CH_3)_2N$–	2–F–	H	H
41	6–C_2H_5O–	H	2–F–	H	H
42	5–CH_3O	6–CH_3NH–	2–F–	H	H
43	4–O_2N–	6–CH_2O–	2–F–	H	H
44	5–Cl–	7–Cl–	2–F–	H	H
45	5–CH_3O–	6–CH_3O–	2–F–	H	H
46	5–Cl	H	3–F–	H	H
47	6–Cl	H	3–F–	H	H
48	7–Cl	H	3–F–	H	H
49	6–$(CH_3)_2N$–	H	3–F–	H	H
50	5–CH_3O–	H	3–F–	H	H
51	6–CH_3O–	H	3–F–	H	H
52	5–CH_3S–	H	3–F–	H	H
53	5–O_2N–	H	3–F–	H	H
54	6–O_2N–	H	3–F–	H	H
55	5–Cl	6–Cl	3–F–	H	H
56	5–C_3H_7	H	3–F–	H	H
57	5–$(CH_3)_2N$–	6–$(CH_3)_2N$–	3–F–	H	H
58	5–Cl	6–$(CH_3)_2N$–	3–F–	H	H
59	4–CH_3O–	6–Cl–	3–F–	H	H
60	4–Cl–	6–Cl –	3–F–	H	H
61	5–CH_3O–	6–$(CH_3)_2N$–	3–F–	H	H
62	6–C_2H_5O–	H	3–F–	H	H
63	5–CH_2O–	6–CH_3NH–	3–F–	H	H

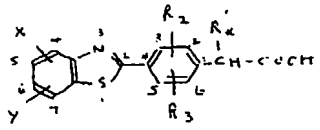


TABLE I (Continued)

Example	X	Y	R_2	R_1	R_α
64	4–O_2N–	6–CH_3O–	3–F–	H	H
65	5–Cl–	7–Cl–	3–F–	H	H
66	5–CH_3O–	6–CH_3O–	3–F–	H	H
67	H	H	3–F–	H	H
68	H	H	3–NH_2–	H	H
69	5–Cl	H	2–NH_2–	H	H
70	6–Cl	H	3–Cl	H	H
71	7–Cl	H	2–Cl	H	H
72	6–$(CH_3)_2N$–	H	2–$(CH_3)_2N$–	H	H
73	5–CH_3O–	H	3–HS–	H	H
74	6–CH_3O–	H	3–CH_3O–	H	H
75	5–CH_3S–	H	2–CH_3O–	H	H
76	5–O_2N–	H	2–CH_3S–	H	H
77	6–O_2N–	H	3–O_2N_2–	H	H
78	5–Cl	6–Cl	2–O_2N–	H	H
79	5–C_3H_7–	H	3–Cl	6–Cl–	H
80	5–$(CH_3)_2N$–	6–$(CH_3)_2N$–	2–Cl–	6–Cl–	H
81	5–Cl	6–$(CH_3)_2N$–	3–CH_3O–	5–CH_3O–	H
82	4–CH_3O–	6–Cl–	3–CH_3O–	6–CH_3O–	H
83	4–Cl–	6–Cl–	2–CH_3O–	6–CH_3O–	
84	5–CH_3O–	6–$(CH_3)_2N$–	2–O_2N–	6–O_2N–	H
85	6–C_2H_5O–	H	2–O_2N–	3–O_2N–	H
86	5–CH_3O–	6–CH_3NH–	3–O_2N–	5–O_2N–	H
87	4–O_2N–	6–CH_3O–	2–O_2N–	6–O_2N	H
88	5–Cl–	7–Cl–	3–HO–	5–HO–	H
89	5–CH_3O–	6–CH_3O–	3–HO–	6–HO–	H
90	H	H	3–H_2N–	6–H_2N–	H
91	H	H	2–H_2N–	6–H_2N–	H
92	H	H	2–C_2H_5O–	3–O_2N–	H
93	H	H	2–H_2N–	6–F–	H

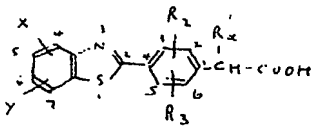


TABLE I (Continued)

Example	X	Y	R_2	R_4	R'_α
94	H	H	2–F–	6–O_2N–	H
95	H	H	2–CH_3O–	3–O_2N–	H
96	H	H	3–C_2H_5O–	6–Cl–	H
97	H	H	3–CH_3O–	6–Cl–	H
98	H	H	2–H_2NSO_2–	H	H
99	H	H	3–H_2NSO_2–	H	H
100	H	H	2–HO_3S–	H	H
101	H	H	3–HO_3S–	H	H
102	H	H	2–CH_3CONH–	H	H
103	H	H	3–CH_3CONH–	H	H
104	H	H	3–C_2H_5O–	H	H
105	H	H	2–CH_3S–	H	H

EXAMPLE 106.

Methyl 4-(benzothiazol-2-yl)-2-fluorophenyl acetate

To a solution of diazomethane in 75 ml. of ether is added portionwise, as a solid, 1.0 gm. of 4-(benzothiazol-2-yl)-2-fluorophenyl acetic acid. Nitrogen is evolved and after 1 hour the excess of diazomethane is consumed by adding acetic acid. The reaction mixture is filtered and the filtrate is concentrated to a solid. Recrystallization from methanol gives methyl 4-(benzothiazol-2-yl)-2-fluorophenyl acetate, m.p. 98—100°C.

Methyl esters and others may also be prepared using well known techniques, for example treating the carboxylic acid with an alcohol in the presence of an acid, or conversion of the carboxylic acid to an acid halide, usually the chloride, and reaction of the acid halide with an alcohol. Representative examples of such esters are:

ethyl 4-(benzothiazol-2-yl)-2-fluorophenylacetate;
allyl 4-(benzothiazol-2-yl)-2-fluorophenylacetate;
cyclopropyl 4-(benzothiazol-2-yl)-phenylacetate;
phenyl 2[4-(benzothiazol-2-yl)phenyl]propionate;
hydroxyethyl 4-(benzothiazol-2-yl)-2-fluorophenylacetate;
diethylaminoethyl 4-(benzothiazol-2-yl)-2-fluorophenylacetate;
benzyl 4-(benzothiazol-2-yl)-2-fluorophenylacetate.

EXAMPLE 107.

4-(Benzothiazol-2-yl)phenylacetamide

A solution of 0.1 gm. of 4-(benzothiazol-2-yl)-phenylacetonitrile (from Example 1, Step A) in 2 ml. of concentrated hydrochloric acid is allowed to stand at room temperature overnight. The reaction mixture is then filtered through a sintered glass filter into 50 ml. of cold water. The resulting precipitate is collected and air dried to give 4-(benzothiazol-2-yl)phenylacetamide.

The amide of any of the other carboxylic acids of this invention can be similarly prepared from the intermediate acetonitriles.

Substituted amides may be conveniently prepared using well known techniques. For example, the carboxylic acids are converted to the acid halide, usually the chloride, and subsequently treated with the appropriate amine. Representative examples include the following:

N-methyl-4-(benzothiazol-2-yl)phenylacetamide;
N-phenyl-4-(benzothiazol-2-yl)-2-fluorophenylacetamide;
N-phenyl-N-methyl-2-[4-(benzothiazol-2-yl)phenyl]propionamide;
N,N-dimethyl-4-(benzothiazol-2-yl)-phenylacetamide;
N-cyclohexyl-4-(benzothiazol-2-yl)-2-fluorophenylacetamide.

EXAMPLE 108.

4-Benzothiazol-2-ylatropic acid

Step A: *Preparation of 4-carboxy-α-hydroxylhydratropamide*

0.1 mole of *p*-acetylbenzoic acid and 30 ml of liquid hydrogen cyanide are stirred at 0°C. for 5 minutes. There is then added 5 ml. of piperidine and the resulting mixture stirred at 0°C. for 1½ hours. The mixture is then poured into 250 ml. of concentrated hydrochloric acid (previously cooled to 0°C.), saturated with hydrogen chloride gas and stirred cold for 1 hour and then at room temperature overnight. Extraction with chloroform, washing the chloroform extracts with water, drying and concentrating *in vacuo*, gives *p*-carboxy-α-hydroxyhydratropamide.

Step B: *Preparation of 4-carboxyatropamide*

To a solution of 0.05 mole of *p*-carboxy-α-hydroxyhydratropamide in 50 cc. of concentrated sulfuric acid. The mixture is heated on the steam bath for half an hour, then concentrated *in vacuo*. Addition of water to the residue and filtration gives *p*-carboxyatropamide.

Step C: *Preparation of 4-benzothiazol-2-ylatropamide*

By the procedure of Example 1, Step A, but substituting for the *p*-cyanomethylbenzoic acid, an equivalent amount of 4-carboxyatropamide, there is produced 4-benzothiazol-2-ylatropamide.

Step D: *Preparation of 4-benzothiazol-2-ylatropic acid*

A mixture of 0.01 mole of 4-benzothiazol-2-yl-atropamide, 15 ml. of acetic acid and 15 ml. of concentrated hydrochloric acid is heated on the steam bath for 1 hour. Filtration of the reaction mixture into 200 ml. of cold water, followed by filtration of the resulting precipitate, gives 4-benzothiazol-2-ylatropic acid.

EXAMPLE 109.

4-(5-Methylsulfinylbenzothiazol-2-yl)phenylacetic acid

To a solution of 3.15 g. (0.01 mole) of 4-(5-methylthiobenzothiazol-2-yl)phenyl acetic acid (from Example 10) in 25 ml. of glacial acetic acid is added 1.2 ml. (0.01 mole) of 30% hydrogen perioxide. The mixture is allowed to stand at ambient temperature overnight. The solution is concentrated to dryness and the residue is crystallized from methanol to give 4-(5-methylsulfinylbenzothiazol-2-yl)phenyl acetic acid.

EXAMPLE 110.

4-(5-Methylsulfonylbenzothiazol-2-yl)phenylacetic acid

By the procedure described in Example 109, but using 0.02 mole of hydrogen peroxide and warming the mixture at reflux for 1—2 hours after standing overnight, there is produced 4-(5-methylsulfonylbenzothiazol-2-yl)phenyl acetic acid.

EXAMPLE 111.

4-(Benzothiazol-2-yl)-2-methylsulfinylphenylacetic acid

To a solution of 3.15 g. (0.01 mole) of 4-(benzothiazol-2-yl)-2-methylthiophenylacetic acid from Example 105 in 25 ml. of glacial acetic acid is added 1.2 ml. (0.01 mole) of 30% hydrogen peroxide. The mixture is allowed to stand overnight at ambient temperature. The solution is concentrated to dryness and the residue is crystallized from methanol to give 4-(benzothiazol-2-yl)-2-methylsulfinylphenylacetic acid.

EXAMPLE 112.

4-(Benzothiazol-2-yl)-2-methylsulfonylphenylacetic acid

By the procedure described in Example 111, but using 0.02 mole of hydrogen peroxide and warming at reflux for 1—2 hours after standing overnight, there is produced 4-(5-benzothiazol-2-yl)-2-methylsulfonylphenylacetic acid.

EXAMPLE 113.

4-(6-Aminobenzothiazol-2-yl)-3-fluorophenylacetic acid

A solution of 3.14 g. (0.01 mole) of 4-(6-nitrobenzothiazol-2-yl)-3-fluorophenylacetic acid (from Example 54) in 100 ml. of ethanol is reacted with hydrogen at room temperature and about 40 p.s.i. in the presence of 10% palladium-on-carbon catalyst until the theoretical quantity of hydrogen has been consumed. The catalyst is removed by filtration and the filtrate is concentrated to dryness. The residue is crystallized from methanol to give 4-(6-aminobenzothiazol-2-yl)-3-fluorophenylacetic acid.

The following are illustrative of techniques for the preparation of pharmaceutical formulations in accordance with the invention. All parts are by weight and mesh sizes are U.S. standards.

EXAMPLE 114.

A mixture of 250 parts of 4-(benzothiazol-2-yl)-2-fluorophenylacetic acid and 25 parts of lactose is granulated with a suitable amount of water, and to this is added 100 parts of maize starch. The mass is passed through a 16-mesh screen. The granules are dried at a temperature below 60°C. The dry granules are passed through a 16-mesh screen and mixed with 3.8 parts of magnesium stearate. They are then compressed into tablets suitable for oral administration.

The specific benzothiazole used in the foregoing example may be replaced by 25, 100, 250, or 500 parts of other benzothiazoles of this invention to produce tablets suitable for oral administration as an anti-inflammatory, antipyretic and/or analgesic according to the method of this invention.

EXAMPLE 115.

A mixture of 50 parts of 4-(benzothiazol-2-yl)-2-fluorophenylacetic acid, 3 parts of the calcium salt of lignin sulphonic acid, and 237 parts of water is ball-milled until the size of substantially all of the particles of the acid is less than 10 microns. The suspension is diluted with a solution containing 3 parts of sodium carboxymethylcellulose and 0.9 parts of the butyl ester of *p*-hydroxybenzoic acid in 300 parts of water. There is thus obtained an aqueous suspension suitable for oral administration for therapeutic purposes.

EXAMPLE 116.

A mixture of 250 parts of 2-[4-(benzothiazol-2-yl)phenyl]propionic acid, 200 parts of maize starch and 30 parts of alginic acid is mixed with a sufficient quantity of 10% aqueous paste of maize starch, and granulated. The granules are dried in a current of warm air and the dry granules are then passed through a 16-mesh screen, mixed with 6 parts of magnesium stearate and compressed into tablet form to obtain tablets suitable for oral administration.

EXAMPLE 117.

A mixture of 500 parts 4-(benzothiazol-2-yl)phenylacetic acid, 60 parts maize starch and 20 parts of gum acacia is granulated with a sufficient quantity of water. The mass is passed through a 12-mesh screen and the granules are dried in a current of warm air. The dry granules are passed through a 16-mesh screen, mixed with 5 parts of magnesium stearate and compressed into tablet form suitable for oral administration.

EXAMPLE 118.

(1) Tablets.—10,000 scored tablets for oral use, each containing 500 mg. of active ingredient are prepared from the following ingredients:

	gm.
4-(benzothiazol-2-yl)-2-fluorophenyl acetic acid	5000
Starch, U.S.P.	350
Talc, U.S.P.	250
Calcium stearate	35

The powdered phenylacetic acid is granulated with a 4% w/v aqueous solution of methylcellulose U.S.P. (1500 cps.). To the dried granules is added a mixture of the remainder of the ingredients and the final mixture compressed into tablets of proper weight.

(2) Capsules.—10,000 two-piece hard gelatine capsules for oral use, each containing 250 mg. of benzothiazole are prepared from the following ingredients:

	gm.
2[4-(benzothiazol-2-yl)phenyl]propionic acid	2500
Lactose, U.S.P.	1000
Starch, U.S.P.	300
Talc, U.S.P.	65
Calcium stearate	25

The powdered benzothiazole is mixed with the starch-lactose mixture followed by the talc and calcium stearate. The final mixture is then encapsulated in the usual manner. Capsules containing 10, 25, 50, and 100 mg. of benzothiazole are also prepared by substituting 100, 250, 500 and 1000 gm. for 2500 gm. in the above formulation.

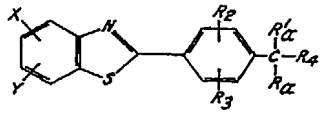
(3) Soft elastic capsules.—One-piece soft elastic capsules for oral use, each containing 200 mg. of benzothiazole are prepared in the usual manner by first dispersing the powdered active material in sufficient corn oil to render the material capsulatable.

(4) Aqueous suspension.—An aqueous suspension for oral use containing in each 5 ml., 1 gram of a 4-(benzothiazol-2-yl)-2-fluorophenylacetic acid is prepared from the following ingredients:

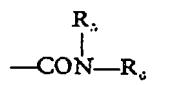
	gm.
4-(benzothiazol-2-yl)-2-fluorophenylacetic acid	2000
Methylparaben, U.S.P.	7.5
Propylparaben, U.S.P.	2.5
Saccharin sodium	12.5
Glycerin	3000
Tragacanth powder	10
Orange oil flavor	10
F. D. and C. orange dye	7.5
Deionized water, q.s. to 10,000 ml.	

WHAT WE CLAIM IS:—

1. A compound of structural formula:



in which R_1' is a hydrogen atom or a C_{1-3} alkyl radical and R_α is a hydrogen atom or R_1' and R_1 together represent a methylene or C_{2-7} alkylidene radical; R_2 is a hydrogen or halogen atom or a hydroxy, C_{1-3} alkoxy, mercapto, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, nitro, amino, di(C_{1-3} alkyl)amino, C_{1-3} alkanoylamino, sulfamoyl, or sulfo radical; R_3 is a hydrogen or halogen atom or a C_{1-3} alkoxy, nitro, hydroxy, or amino radical; X is a hydrogen or halogen atom or a di(C_{1-3} alkyl)amino, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, nitro, amino, or C_{1-3} alkyl radical; Y is a hydrogen or halogen atom or a di(C_{1-3} alkyl)amino, C_{1-3} alkylamino, or C_{1-3} alkoxy radical; R_1 is a carboxy or hydroxymethyl radical or a radical of formula —COOR, —COOM or



where R is C_{1-3} alkyl, C_{3-5} alkenyl, C_{3-7} cycloalkyl, phenyl, phenyl-(C_{1-3} alkyl), (C_{1-3} alkoxy)-(C_{1-3} alkyl), C_{1-3} hydroxyalkyl, or di(C_{1-3} alkyl)amino-(C_{1-3} alkyl) radical; M is a pharmaceutically acceptable non-toxic anion; R_5 is a hydrogen atom or a C_{1-3} alkyl, phenyl-(C_{1-3} alkyl), phenyl, or C_{3-7} cycloalkyl radical and R_6 is a hydrogen atom or a C_{1-3} alkyl radical, provided that R_1 is not —COOH or —$CONH_2$ when X, Y, R_2, R_3, R_α and R_1' are all hydrogen.

2. A compound as claimed in Claim 1 in which each of R_2 and R_3 is a hydrogen or halogen atom.

3. A compound as claimed in Claim 2 in which R_a' is hydrogen or methyl; R_a is hydrogen; X is a hydrogen or halogen atom or a C_{1-3} alkoxy or C_{1-3} alkyl radical; Y is hydrogen, halogen or C_{1-3} alkoxy; and R_4 is —COOH, —COOR or —$CONR_5R_6$.

4. A compound as claimed in Claim 3 in which X and Y are both hydrogen atoms.

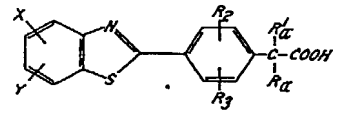
5. 4-(Benzothiazol-2-yl)-2-fluorophenylacetic acid.

6. 2-[4-(Benzothiazol-2-yl)phenyl]propionic acid.

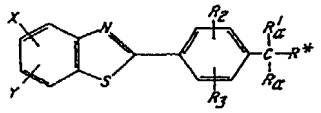
7. *d*-2-[4-(Benzothiazol-2-yl)phenyl]propionic acid.

8. 4-(Benzothiazol-2-yl)-3-fluorophenylacetic acid.

9. A method of preparing a compound of structural formula:

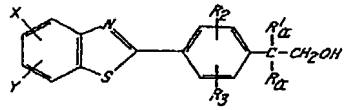


in which R_a, R_a', X, Y, R_2 and R_3 are as defined in Claim 1, that comprises hydrolysing a compound of structural formula:



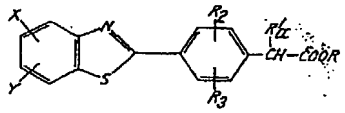
where R* is —CN when R_a is hydrogen and is —$CONH_2$ when R_a and R_a' together represent alkylidene.

10. A method as claimed in Claim 9 including the further step of reducing the product to produce a compound of formula:



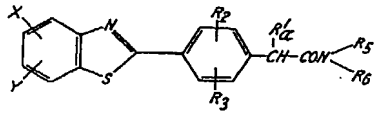
where R_a', R_a, R_2, R_3, X and Y are as defined in Claim 1.

11. A method as claimed in Claim 9 including the further step of esterifying the product to produce a compound of formula:



where R, R_a', R_2, R_3, X and Y are as defined in Claim 1.

12. A method as claimed in Claim 9 including the further step of amidating the product to produce a compound of formula:



where R_a', R_2, R_3, R_5, R_6, X and Y are as defined in Claim 1.

13. A method as claimed in any one of Claims 9—12 in which R_a is hydrogen and each of R_5 and R_6, which are similar or dissimilar, is a hydrogen or halogen atom.

14. A method as claimed in Claim 13 in which R′ is hydrogen or methyl; X is hydrogen, halogen, C alkoxy or C alkyl and Y is hydrogen, halogen or C alkoxy.

15. A method as claimed in Claim 14 in which X and Y are both hydrogen atoms.

16. A method as claimed in Claim 9 in which R_1, R′, X, Y and R_3 are hydrogen and R_2 is fluoro and the product is 4-(benzothiazol-2-yl)-2-fluorophenylacetic acid.

17. A method as claimed in Claim 9 in which R_1, R′, R_2, R_3, X and Y are hydrogen and the product is 4-(benzothiazolyl-2-yl)phenylacetic acid.

18. A method as claimed in Claim 9 in which R_1, R_2, R_3, X and Y are hydrogen, and R′ is methyl, and the product is 2-[4-(benzothiazol-2-yl)-phenyl]propionic acid.

19. A method as claimed in Claim 9 in which R_1, R′, R_3, X and Y are hydrogen and R_2 is fluoro and the product is 4-(benzothiazol-2-yl)-3-fluorophenylacetic acid.

20. A pharmaceutical composition comprising as active ingredient a compound as claimed in any one of Claims 1—8 and a non-toxic pharmaceutically acceptable carrier, adjuvant or vehicle.

21. A composition as claimed in Claim 20 in the form of a tablet, troche, lozenge, aqueous or oily suspension, dispersible powder or granules, emulsion, hard or soft capsule, syrup, elixir, sterile injectable preparation, suppository, cream, ointment or jelly.

22. A pharmaceutical composition containing as active ingredient 4-(benzothiazol-2-yl)phenylacetic acid and a non-toxic pharmaceutically acceptable carrier, adjuvant or vehicle, the composition being in the form of a tablet, troche, lozenge, aqueous or oily suspension, dispersible powder or granules, emulsion, hard or soft capsule, syrup, elixir, sterile injectable preparation, suppository, cream, ointment or jelly.

23. A method of preparing a compound as claimed in claim 1, substantially as hereinbefore described in any one of Examples 2—113.

24. A compound as claimed in claim 1, when prepared by a method as claimed in any one of claims 9—19 or an obvious chemical equivalent of such a method.

25. A pharmaceutical composition as claimed in claim 20 or 22, substantially as hereinbefore described in any one of Examples 114—118.

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